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☐ 1. Document ID: US 6268200 B1

L2: Entry 1 of 5 File: USPT Jul 31, 2001

US-PAT-NO: 6268200
DOCUMENT-IDENTIFIER: US 6268200 B1

TITLE: Biotherapeutic virus attenuation using variable frequency microwave energy

DATE-ISSUED: July 31, 2001

INVENTOR-INFORMATION: NAME	CITY	STATE	ZIP CODE	COUNTRY
Tucker; Denise A.	Raleigh	NC	N/A	N/A
Lundblad; Roger Lauren	Chapel Hill	NC	N/A	N/A
Reisner; Howard M.	Durham	NC	N/A	N/A
Kingdon; Henry Shannon	Lake Forest	IL	N/A	N/A

US-CL-CURRENT: 435/236; 422/21, 435/1.1, 435/173.3, 435/2, 435/235.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

☐ 2. Document ID: US 5955269 A

L2: Entry 2 of 5 File: USPT Sep 21, 1999

US-PAT-NO: 5955269
DOCUMENT-IDENTIFIER: US 5955269 A

TITLE: Methods of screening foods for nutraceuticals

DATE-ISSUED: September 21, 1999

INVENTOR-INFORMATION: NAME	CITY	STATE	ZIP CODE	COUNTRY
Ghai; Geetha	Murray Hill	NJ	N/A	N/A
Boyd; Charles	New Brunswick	NJ	N/A	N/A
Csiszar; Katalin	New Brunswick	NJ	N/A	N/A
Ho; Chi-Tang	East Brunswick	NJ	N/A	N/A
Rosen; Robert T.	Pottersville	NJ	N/A	N/A

US-CL-CURRENT: 435/6; 426/478, 435/4, 435/91.2

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw. Desc | Image

☐ 3. Document ID: US 5795972 A File: USPT Aug 18, 1998

L2: Entry 3 of 5

US-PAT-NO: 5795972
DOCUMENT-IDENTIFIER: US 5795972 A

TITLE: Chimeric mutational vectors having non-natural nucleotides

DATE-ISSUED: August 18, 1998

INVENTOR-INFORMATION:				
NAME	CITY	STATE	ZIP CODE	COUNTRY
Kmiec; Eric B.	Malvern	PA	N/A	N/A

US-CL-CURRENT: 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWMC | Draw Desc | Image

☐ 4. Document ID: US 5731181 A File: USPT Mar 24, 1998

L2: Entry 4 of 5

US-PAT-NO: 5731181
DOCUMENT-IDENTIFIER: US 5731181 A

TITLE: Chimeric mutational vectors having non-natural nucleotides

DATE-ISSUED: March 24, 1998

INVENTOR-INFORMATION:				
NAME	CITY	STATE	ZIP CODE	COUNTRY
Kmiec; Eric B.	Malvern	PA	N/A	N/A

US-CL-CURRENT: 435/6; 435/463, 536/23.1

Full | Title | Citation | Front | Review | Classification | Date | Reference | KWMC | Draw Desc | Image

☐ 5. Document ID: US 5407581 A File: USPT Apr 18, 1995

L2: Entry 5 of 5

US-PAT-NO: 5407581
DOCUMENT-IDENTIFIER: US 5407581 A

TITLE: Filter medium having a limited surface negative charge for treating a blood material

DATE-ISSUED: April 18, 1995

INVENTOR-INFORMATION:				
NAME	CITY	STATE	ZIP CODE	COUNTRY
Onodera; Hirokazu	Oita	N/A	N/A	JPX
Yoshida; Makoto	Oita	N/A	N/A	JPX

US-CL-CURRENT: 210/654; 210/321.69, 210/508, 210/767, 210/929, 502/403

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Term	Documents
HUMAN.DWPI,EPAB,JPAB,USPT,PGPB.	400501
HUMANS.DWPI,EPAB,JPAB,USPT,PGPB.	84127
PORCINE.DWPI,EPAB,JPAB,USPT,PGPB.	10589
PORCINES.DWPI,EPAB,JPAB,USPT,PGPB.	161
PLANT?	0
PLANTA.DWPI,EPAB,JPAB,USPT,PGPB.	2096
PLANTB.DWPI,EPAB,JPAB,USPT,PGPB.	1
PLANTD.DWPI,EPAB,JPAB,USPT,PGPB.	3
PLANTE.DWPI,EPAB,JPAB,USPT,PGPB.	2076
PLANTG.DWPI,EPAB,JPAB,USPT,PGPB.	2
(L1 AND (HUMAN OR PORCINE) AND PLANT?).USPT,PGPB,JPAB,EPAB,DWPI.	5

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HUMAN.DWPI,EPAB,JPAB,USPT,PGPB.	400501
HUMANS.DWPI,EPAB,JPAB,USPT,PGPB.	84127
PORCINE.DWPI,EPAB,JPAB,USPT,PGPB.	10589
PORCINES.DWPI,EPAB,JPAB,USPT,PGPB.	161
PLANT?	0
PLANTA.DWPI,EPAB,JPAB,USPT,PGPB.	2096
PLANTB.DWPI,EPAB,JPAB,USPT,PGPB.	1
PLANTD.DWPI,EPAB,JPAB,USPT,PGPB.	3
PLANTE.DWPI,EPAB,JPAB,USPT,PGPB.	2076
PLANTG.DWPI,EPAB,JPAB,USPT,PGPB.	2
(L1 AND (HUMAN OR PORCINE) AND PLANT?).USPT,PGPB,JPAB,EPAB,DWPI.	5

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IBM Technical Disclosure Bulletins

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Search History

Today's Date: 9/19/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	l1 and (human or porcine) and plant?	5	L2
USPT,PGPB,JPAB,EPAB,DWPI	coagulation factor VIII	386	L1

? t s13/3,ab/all

>>>No matching display code(s) found in file(s): 65, 306

13/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09846229 98342257 PMID: 9675055
The corn inhibitor of activated Hageman factor: purification and properties of two recombinant forms of the protein.
Hazegh-Azam M; Kim SS; Masoud S; Andersson L; White F; Johnson L; Muthukrishnan S; Reeck G
Department of Biochemistry, Kansas State University, Manhattan, Kansas, 66503, USA.
Protein expression and purification (UNITED STATES) Jul 1998, 13 (2) p143-9, ISSN 1046-5928 Journal Code: BJV
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A cDNA clone that encodes the 14-kDa bifunctional inhibitor from corn seeds (L. Wen et al., **Plant** Mol. Biol. 18, 813-814, 1992) has been expressed in Escherichia coli after being incorporated into the pT7 expression vector. This inhibitor protein, referred to as CHFI (for the corn inhibitor of activated Hageman factor) or as the popcorn inhibitor, is an important tool for specific inhibition of human activated Hageman factor (activated forms of **coagulation Factor** XII) and has been well characterized as isolated from corn seeds. Recombinant CHFI was expressed in E. coli in high levels but was insoluble. We solubilized the expressed protein by sonication in 5 M urea and 1% Triton X-100. Several steps of purification, culminating with reversed-phase HPLC, yielded pure, recombinant corn inhibitor in about 5% yield (about 1 mg per liter of culture). The form with which we have worked most, 7N-CHFI, contains 7 amino acid residues at its N-terminus that are encoded by the expression vector. Physical properties of this recombinant protein indicate it has the expected mass and is properly folded. Functionally, 7N-CHFI is indistinguishable from the inhibitor isolated from corn seeds in its inhibition of **porcine** trypsin, human beta-Factor XIIa, failure to inhibit human plasma kallikrein, and its inhibition of an insect alpha-amylase. A second recombinant form, (4N-11)-CHFI, which lacks 11 residues from the corn inhibitor's N-terminus, is indistinguishable from 7N-CHFI in its pattern of inhibition of the three test proteinases but is inactive against the insect alpha-amylase. This suggests that the N-terminal region of 7N-CHFI forms at least part of the protein's site of interaction with alpha-amylase. Copyright 1998 Academic Press.
? ds

Set	Items	Description
S1	85	HUMAN (W) COAGULATION (W) FACTOR (W) VIII
S2	2	S1 AND PLANT?
S3	2	RD (unique items)
S4	0	S1 AND VIIIA AND B (W) DOMAIN
S5	1	HUMAN (W) COAGULATION (W) FACTOR (W) VIII AND B-DOMAIN
S6	9	HUMAN (W) COAGULATION (W) FACTOR (W) VIII AND B (W)DOMAIN
S7	8	S6 NOT S5
S8	3	RD (unique items)
S9	3	HUMAN (W) COAGULATION (W) FACTOR (W) VIIIA
S10	2	RD (unique items)
S11	342	PORCINE AND COAGULATION (W) FACTOR

S12 3 S11 AND PLANT?
S13 1 RD (unique items)
? s s11 and VIII

342 S11
93014 VIII
S14 184 S11 AND VIII
? s s14 and a2

184 S14
117014 A2
S15 42 S14 AND A2
? s s15 and (chimera)

42 S15
26553 CHIMERA
S16 0 S15 AND (CHIMERA)
? s s15 and human/

>>>Possible typing error near end of line
? s s15 and human?

Processing
Processed 10 of 20 files ...
Completed processing all files
42 S15
19807519 HUMAN?
S17 27 S15 AND HUMAN?
? rd

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>>>Records from unsupported files will be retained in the RD set.
...completed examining records
S18 16 RD (unique items)
? t s18/3,ab/all

>>>No matching display code(s) found in file(s): 65, 306

18/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08588020 95301538 PMID: 7540171
Residues 484-508 contain a major determinant of the inhibitory epitope in the **A2** domain of **human** factor **VIII**.
Healey JF; Lubin IM; Nakai H; Saenko EL; Hoyer LW; Scandella D; Lollar P
Emory University, Atlanta, Georgia 30322, USA.
Journal of biological chemistry (UNITED STATES) Jun 16 1995, 270 (24) p14505-9, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: P50-HL44336, HL, NHLBI; R01-HL36094, HL, NHLBI; R01-HL46215, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The **A2** domain (residues 373-740) of **human** blood **coagulation factor VIII** (fVIII) contains a major epitope for inhibitory alloantibodies and autoantibodies. We took advantage of the differential reactivity of inhibitory antibodies with **human** and **porcine** fVIII and mapped a major determinant of the **A2** epitope by using a series of active recombinant hybrid **human/porcine** fVIII molecules. Hybrids containing a substitution of **porcine** sequence at segment 410-508, 445-508, or 484-508 of the **human** **A2** domain were not inhibited by a murine monoclonal antibody **A2** inhibitory, mAb 413, whereas hybrids containing substitutions at 387-403, 387-444, and 387-468 were inhibited by mAb 413. This indicates that the

segment bounded by Arg484 and Ile508 contains a major determinant of the **A2** epitope. mAb 413 did not inhibit two more hybrids that contained **porcine** substitutions at residues 484-488 and 489-508, indicating that amino acid side chains on both sides of the Ser488-Arg489 bond within the Arg484-Ile508 segment contribute to the **A2** epitope. The 484-508, 484-488, and 489-508 **porcine** substitution hybrids displayed decreased inhibition by **A2** inhibitors from four patient plasmas, suggesting that there is little variation in the structure of the **A2** epitope in the inhibitor population.

18/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08375051 94179260 PMID: 7510693
Elimination of a major inhibitor epitope in factor **VIII**.
Lubin IM; Healey JF; Scandella D; Runge MS; Lollar P
Department of Medicine, Emory University, Atlanta, Georgia 30322.
Journal of biological chemistry (UNITED STATES) Mar 25 1994, 269 (12) p8639-41, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: P50-HL44336, HL, NHLBI; R01-HL36094, HL, NHLBI; R01-HL46215, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

The **A2** and C2 domains of **human** blood **coagulation factor VIII** (fVIII) contain the epitopes targeted by most inhibitory allo- and autoantibodies. **Human** inhibitors usually display limited or no reaction with **porcine** fVIII. We constructed an active, recombinant hybrid **human/porcine** fVIII molecule by replacing the putative **human** fVIII **A2** domain epitope with the homologous **porcine** sequence. The hybrid retained full activity in the presence of antibodies with specificity restricted to the **human A2** epitope. In contrast, the hybrid was neutralized by an anti-C2 antibody. These findings provide a basis for fine epitope mapping and for therapy of the inhibitor patient.

18/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07668993 93054719 PMID: 1429706
Coagulant properties of hybrid **human/porcine** factor **VIII** molecules.
Lollar P; Parker ET; Fay PJ
Department of Medicine, Emory University, Atlanta, Georgia 30322.
Journal of biological chemistry (UNITED STATES) Nov 25 1992, 267 (33) p23652-7, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: HL-38199, HL, NHLBI; HL-40921, HL, NHLBI; HL-46215, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed

Human and **porcine** factor **VIII** (fVIII) are activated by thrombin to form a heterotrimer composed of subunits designated A1 and **A2** derived from the fVIII heavy chain (HC) and a subunit designated A3-C1-C2 derived from the fVIII light chain (LC). **Human** and **porcine** fVIII were activated at the same rate to the same peak levels but dissociation of the **A2** subunit and concomitant loss of fVIIIa activity at pH 7.4 and 22 degrees C was 3-fold faster with **human** fVIIIa compared to **porcine** fVIIIa (0.35 min-1 versus 0.12 min-1, respectively). To determine structural requirements for the increased activity of **porcine** fVIII, plasma-derived hybrid **human/porcine** fVIII molecules were isolated. **Porcine** HC/**human** LC (pHC/hLC) fVIII had 44-fold higher coagulant activity than reconstituted

human fVIII (hHC/hLC), [redacted]0-fold higher activity than hHC/pLC, and slightly (1.4-fold) hig[redacted] activity than reconstituted p[redacted]**ine** fVIII (pHC/pLC). Additionally, **human** and **porcine A2** subunits and inactive A1/A3-C1-C2 **human** and **porcine** dimers were isolated and reconstitution experiments were done. Addition of the **porcine A2** subunit to the **human** A1/A3-C1-C2 dimer produced coagulant activity similar to that found with **porcine** fVIIIa and superior to **human** fVIIIa. These results suggest that **human** fVIII has weaker coagulant activity than **porcine** fVIII due to faster dissociation of the **A2** subunit and that the **A2** subunit itself is responsible for the difference.

18/3,AB/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

09291503 Genuine Article#: 388JL Number of References: 32
Title: Antigenicity of putative phospholipid membrane-binding residues in factor **VIII** (ABSTRACT AVAILABLE)
Author(s): Barrow RT; Healey JF; Jacquemin MG; Saint-Remy JMR; Lollar P (REPRINT)
Corporate Source: Emory Univ,Winship Canc Inst,1639 Pierce DR,Rm 1003,Woodruff Mem Bldg/Atlanta//GA/30322 (REPRINT); Emory Univ,Winship Canc Inst,Atlanta//GA/30322; Katholieke Univ Leuven,Ctr Mol & Vasc Biol,Louvain//Belgium/
Journal: BLOOD, 2001, V97, N1 (JAN 1), P169-174
ISSN: 0006-4971 Publication date: 20010101
Publisher: AMER SOC HEMATOLOGY, 1900 M STREET. NW SUITE 200, WASHINGTON, DC 20036 USA
Language: English Document Type: ARTICLE
Abstract: Most inhibitory antibodies to **human** factor **VIII** (fVIII) bind to epitopes in the **A2**, ap-A3, or C2 domains. The anticoagulant action of antibodies to the C2 domain is due to inhibition of binding of fVIII to phospholipid. The x-ray structure of the **human** fVIII C2 domain shows a putative hydrophobic, 3-prong, phospholipid membrane-binding site consisting of Met2199/Phe2200, Val2223, and Leu2251/Leu2252. Additionally, Lys2227, near Val2223, is part of a ring of positively charged residues that may contribute to electrostatic interaction of fVIII with negatively charged phosphatidylserine. In this study, 8 active mutants of **human** fVIII (Met2199Ile, Leu2252Phe, Phe220Leu, Val2223Ala, Lys2227Glu, Met2199Ile/Phe2200Leu, Val2223Ala/Lys2227Glu, and Met2199Ile/Phe2200Leu/Val2223Ala/Lys2227Glu), which were constructed on the basis of differences between **human**, **porcine**, murine, end canine fVIII at proposed phospholipid binding sites, were expressed. The antigenicity of the mutants toward 5 C2-specific polyclonal **human** antibodies was measured by using the Bethesda assay, A **human** monoclonal anti-C2 antibody, BO2C11, and a murine CS-specific monoclonal antibody, NMC **VIII**-5, were also included in the analysis. In comparison with wild-type, B-domainless fVIII, the Met2199Ile, Phe2200Leu, and Leu2252 single mutants had lower antigenicity toward most of the inhibitors. In contrast, the Val2223Ala and Lys2227Glu mutants usually showed increased antigenicity. These results suggest that C2 inhibitors frequently target the Met2199/Phe2200 and Leu2251/Leu2252 beta -hairpins and are consistent with the hypothesis that these residues participate in binding to phospholipid membranes. In contrast, Val2223Ala and Lys2227 may oppose antibody binding sterically or through stabilization of a low-affinity membrane-binding conformation of the C2 domain. (C) 2001 by The American Society of Hematology.

18/3,AB/5 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05328789 Genuine Article#: VQ679 Number of References: 45
Title: SLOWED RELEASE OF THROMBIN-CLEAVED FACTOR-**VIII** FROM VON-WILLEBRAND-FACTOR BY A MONOCLONAL AND A **HUMAN**-ANTIBODY IS A NOVEL MECHANISM FOR FACTOR-**VIII** INHIBITION (Abstract Available)
Author(s): SAENKO EL; SHIMA M; GILBERT M; SCANDELLA D
Corporate Source: AMER RED CROSS,HOLLAND LAB,15601 CRABBS BRANCH WAY/ROCKVILLE//MD/20855; AMER RED CROSS,HOLLAND LAB/ROCKVILLE//MD/20855 ; NARA MED UNIV,DEPT PEDIAT/NARA//JAPAN/; BRIGHAM & WOMENS HOSP,BROCKTON W ROXBURY VET AFFAIRS MED CTR/BOSTON//MA/02115; HARVARD UNIV,SCH MED/BOSTON//MA/02115
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1996, V271, N44 (NOV 1), P 27424-27431
ISSN: 0021-9258
Language: ENGLISH Document Type: ARTICLE
Abstract: The anti-factor **VIII** (fVIII) C2 domain monoclonal antibody ESH8 inhibits fVIII activity only when fVIII is bound to von Willebrand factor (vWf). However, ESH8 binds with similar affinity to fVIII and fVIII . vWf complex, and it does not affect the kinetics of thrombin cleavage at positions 372 and 740 within the fVIII heavy chain and at 1689 within the light chain, The latter is required for fVIII release from vWf. We showed that ESH8 reduced the initial rate of thrombin-activated fVIII (fVIIIa) release from vWf by 4.3-fold compared to that in the absence of antibody. The complex of vWf . fVIII . ESH8 was activated, and the rate constant determined for fVIIIa dissociation from vWf was 4 x 10(-3) s(-1). We constructed a mathematical. model incorporating the measured rates for fVIIIa release from vWf and for inactivation of heterotrimeric fVIIIa due to the spontaneous loss of the **A2** subunit and found that the decreased release rate is sufficient to explain our experimentally observed inhibition of Nm activity by ESH8. We hypothesize that the slowed rate of fVIIIa release from vWf in the presence of ESH8 allows time for inactivation of unstable fVIIIa prior its participation in the formation of the factor Xase complex, The relevance of these findings is illustrated by our observation that reduction of fVIIIa release from vWf represents an additional mechanism of MII inhibition by an anti-C2 domain antibody (epitope 2218-2307) from a hemophilia A patient. This rare antibody binds to a more amino-terminal epitope than other **human** anti-Ca inhibitors, resulting in its lack of inhibition of fVIII binding to vWf but not to phospholipid. These two MII ligands therefore bind to C2 sites which do not overlap completely.

18/3,AB/6 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04542151 Genuine Article#: TR320 Number of References: 37
Title: THE SEQUENCE GLU(1811)-LYS(1818) OF **HUMAN** BLOOD-**COAGULATION FACTOR-VIII** COMPRISES A BINDING-SITE FOR ACTIVATED FACTOR-IX (Abstract Available)
Author(s): LENTING PJ; VANDELOO JWHP; DONATH MJSH; VANMOURIK JA; MERTENS K
Corporate Source: NETHERLANDS RED CROSS,BLOOD TRANSFUS SERV,CENT LAB,DEPT BLOOD COAGULAT,PLESMANLAAN 125/1066 CX AMSTERDAM//NETHERLANDS/; NETHERLANDS RED CROSS,BLOOD TRANSFUS SERV,CENT LAB,DEPT BLOOD COAGULAT/1066 CX AMSTERDAM//NETHERLANDS/
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1996, V271, N4 (JAN 26), P 1935-1940
ISSN: 0021-9258
Language: ENGLISH Document Type: ARTICLE
Abstract: In previous studies we have shown that the interaction between factors IXa and **VIII** involves the light chain of factor **VIII** and that this interaction is inhibited by the monoclonal antibody CLB-CAg A against the factor **VIII** region

Gln(1778)-Asp(1840) [illegible]nting, P. J., Donath, M. J. S. H., van Mourik, J. A., and Mertens, [illegible](1994) J. Biol. Chem. 269, 715[illegible]155). Employing distinct recombinant factor **VIII** fragments, we now have localized the epitope of this antibody more precisely between the A3 domain residues Glu(1801) and Met(1823). Hydropathy analysis indicated that this region is part of a major hydrophilic exosite within the A3 domain. The interaction of factor IXa with this exosite was studied by employing overlapping synthetic peptides encompassing the factor **VIII** region Tyr(1786)-Ala(1834). Factor IXa binding was found to be particularly efficient to peptides corresponding to the factor **VIII** sequences Lys(1804)-Lys(1818) and Glu(1811)-Gln(1820). The same peptides proved effective in binding antibody CLB-CAg A. Further analysis revealed that peptides Lys(1804)-Lys(1818) and Glu(1811)-Gln(1820) interfere with binding of factor IXa to immobilized factor **VIII** light chain (K-i approximate to 0.2 mM and 0.3 mM respectively). Moreover, these peptides inhibit factor X activation by factor IXa in the presence of factor VIIIa (K-i approximate to 0.2 mM and 0.3 mM, respectively) but not in its absence. Equilibrium binding studies revealed that these two peptides bind to the factor IX zymogen and its activated form, factor IXa, with the same affinity (apparent K-d approximate to 0.2 mM), whereas the complete factor **VIII** light chain displays preferential binding to factor IXa. In conclusion, our results demonstrate that peptides consisting of the factor **VIII** light chain residues Lys(1804)-Lys(1818) and Glu(1811)-Gln(1820) share a factor IXa binding site that is essential for the assembly of the factor X-activating factor IXa-factor VIIIa complex. We propose that the overlapping sequence Glu(1811)-Lys(1818) comprises the minimal requirements for binding to activated factor IX.

18/3,AB/7 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04377360 Genuine Article#: RY460 Number of References: 39
Title: KINETICS OF THE INTERACTION BETWEEN THE **HUMAN** FACTOR VIIIA SUBUNITS - EFFECTS OF PH, IONIC-STRENGTH, CA2+ CONCENTRATION, HEPARIN, AND ACTIVATED PROTEIN C-CATALYZED PROTEOLYSIS (Abstract Available)
Author(s): PERSSON E; EZBAN M; SHYMKO RM
Corporate Source: NOVO NORDISK AS,COAGULAT RES,HAGEDORNSVEJ 1,HAB393/DK-2820 GENTOFTE//DENMARK/; NOVO NORDISK AS,DEPT COAGULAT RES/DK-2820 GENTOFTE//DENMARK/; NOVO NORDISK AS,HAGEDORN RES INST/DK-2820 GENTOFTE//DENMARK/
Journal: BIOCHEMISTRY, 1995, V34, N39 (OCT 3), P12775-12781
ISSN: 0006-2960
Language: ENGLISH Document Type: ARTICLE
Abstract: **Coagulation factor** VIIIa consists of a heterotrimer in which the **A2** subunit is bound to the A1/A3C1C2 dimer. The dissociation of this complex causes the spontaneous and reversible decay of factor VIIIa activity. In order to characterize the kinetics and affinity of the interaction between **A2** and A1/A3C1C2, as well as the influence of different parameters on the interaction, the subunits were chromatographically separated and reassembled in a BIAcore instrument (Pharmacia Biosensor). In the binding experiments, **A2** was free in solution, whereas A1/A3C1C2 was immobilized on the dextran surface by direct coupling or captured on an immobilized monoclonal anti-C2 antibody. At our chosen standard condition (pH = 6.0, I = 0.12, and [Ca2+] = 2 mM), the association rate constant, dissociation rate constant, and resulting equilibrium dissociation constant were ca. 1.4 x 10(4) M(-1) s(-1), 2.1 x 10(-4) s(-1), and 16 nM, respectively. Increasing the ionic strength or Ca2+ concentration resulted in both slower association and faster dissociation. At 0.3 M NaCl or 25 mM Ca2+, the dissociation constant was >1 mu M. This implies that electrostatic forces involved in the interaction contribute at least one-fourth of the total binding energy. Increasing pH caused a

similar effect, yielding a dissociation constant of ca. 0.9 mu M at pH 7.5. In those cases where the equilibrium dissociation constants had been determined from solution phase experiments [Fay, P. J., & Smudzin, T. M. (1992) J. Biol. Chem. 267, 13246-13250; Lollar, P., Parker, E. T., & Fay, P. J. (1992) J. Biol. Chem. 267, 23652-23657], these constants agreed well with our results. In addition, direct immobilization of A1/A3C1C2 or capture on an antibody gave very similar rate constants, indicating that neither the immobilization per se nor the mode of immobilization affected the subunit interaction. Limited proteolysis of A1/A3C1C2 by activated protein C abolished its ability to bind **A2**, supporting the involvement of the negatively charged region containing residues 337-372. Heparin prevented **A2** /A1/A3C1C2 heterotrimer formation, presumably by binding to and blocking basic regions of importance for the interaction.

18/3,AB/8 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

01290652 Genuine Article#: GM039 Number of References: 32
Title: ACTIVATED PROTEIN C-CATALYZED INACTIVATION OF **HUMAN** FACTOR-**VIII** AND FACTOR-**VIII** - IDENTIFICATION OF CLEAVAGE SITES AND CORRELATION OF PROTEOLYSIS WITH COFACTOR ACTIVITY (Abstract Available)
Author(s): FAY PJ; SMUDZIN TM; WALKER FJ
Corporate Source: UNIV ROCHESTER,SCH MED & DENT,MED CTR,DEPT MED,HEMATOL UNIT,POB 610,601 ELMWOOD AVE/ROCHESTER//NY/14642; UNIV ROCHESTER,SCH MED & DENT,DEPT BIOCHEM/ROCHESTER//NY/14642; UNIV CONNECTICUT,AMER RED CROSS BLOOD SERV/FARMINGTON//CT/06032; UNIV CONNECTICUT,DEPT MED/FARMINGTON//CT/06032; UNIV CONNECTICUT,DEPT LAB MED/FARMINGTON//CT/06032
Journal: JOURNAL OF BIOLOGICAL CHEMISTRY, 1991, V266, N30, P20139-20145
Language: ENGLISH Document Type: ARTICLE
Abstract: **Human** factor **VIII** and factor **VIII**(a) were proteolytically inactivated by activated protein C. Cleavages occurred within the heavy chain (contiguous A1-**A2**-B domains) of factor **VIII** and in the heavy chain-derived A1 and **A2** subunits of factor **VIII**(a), whereas no proteolysis was observed in the light chain or light chain-derived A3-C1-C2 subunit. Reactivity to an anti-**A2** domain monoclonal antibody and NH2-terminal sequence analysis of three terminal digest fragments from factor **VIII** allowed ordering of fragments and identification of cleavage sites. Fragment A1 was derived from the NH2 terminus and resulted from cleavage at Arg336-Met337. The **A2** domain was bisected following cleavage at Arg562-Gly563 and yielded fragments designated A2N and A2C. A third cleavage site is proposed at the **A2**-B junction (Arg740-Ser741) since fragment A2C was of equivalent size when derived either from factor **VIII** or factor **VIII**(a). The site at Arg562 was preferentially cleaved first in factor **VIII**(a) compared with the site at Arg336, and it was this initial cleavage that most closely correlated with the loss of cofactor activity. Factor **VIII**(a) as inactivated 5-fold faster than factor **VIII**, possibly as a result of increased protease utilization of the site at Arg562 when the **A2** subunit is not contiguous with the A1 domain. When initial cleavage occurred at Arg336, it appeared to preclude subsequent cleavage at Arg562, possibly by promoting dissociation of the **A2** domain (subunit) from the A1/light chain dimer. This conclusion was supported by the failure of protease treated A1/A3-C1-C2 dimer to bind **A2** subunit and gel filtration analysis that showed dissociation of the **A2** domain-derived fragments, A2N and A2C, from the A1 fragment/light chain dimer. These results suggest a mechanism for activated protein C-catalyzed inactivation of factor **VIII**(a) involving both covalent alteration and fragment dissociation.

18/3,AB/9 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

02222673 4252216
Analysis of the **human factor VIII A2** inhibitor epitope by alanine scanning mutagenesis
Lubin, I.M.; Healey, J.F.; Barrow, R.T.; Scandella, D.; Lollar, P.
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J. BIOL. CHEM. vol. 272, no. 48, pp. 30191-30195 (1997)
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DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Biochemistry Abstracts 2: Nucleic Acids

Antibodies directed to the **A2** domain of factor **VIII** (fVIII) are usually an important component of the polyclonal response in patients who have clinically significant inhibitory antibodies to fVIII. A major determinant of the **A2** epitope has been located by homolog scanning mutagenesis using recombinant hybrid **human/porcine** fVIII molecules to a sequence bounded by Arg super(484)-Ile super(508). Within this region, **human** residues Arg super(484), Pro super(485), Tyr super(487), Ser super(488), Arg super(489), Pro super(492), Val super(495), Phe super(501), and Ile super(508) differ from **porcine** fVIII. We stably expressed in mammalian cells nine active B-domainless **human** fVIII molecules containing single alanine substitutions at these sites. Their inhibition by a murine anti-**A2** monoclonal antibody, monoclonal antibody (mAb) 413, and by three **A2**-specific alloimmune and two **A2**-specific autoimmune **human** inhibitor plasmas was measured by the Bethesda assay. The inhibition of Arg super(484) arrow right Ala, Tyr super(487) arrow right Ala, Arg super(489) arrow right Ala, and Arg super(492) arrow right Ala by mAb413 was reduced by greater than 90% compared with wild-type, B-domainless **human** fVIII. mAb413 inhibited the most severely affected mutant, Arg super(489) arrow right Ala, 0.01% as well as wild-type fVIII. For all five patient plasmas, the Tyr super(487) arrow right Ala mutant displayed the greatest reduction in inhibition. The inhibition of the Tyr super(487) arrow right Ala mutant by these antibodies ranged from 10% to 20% that of wild-type fVIII. The inhibition of the Ser super(488) arrow right Ala, Arg super(489) arrow right Ala, Pro super(492) arrow right Ala, Val super(495) arrow right Ala, Phe super(501) arrow right Ala, and Ile super(508) arrow right Ala mutants by most of the plasmas also was significantly reduced. In contrast, the Arg super(484) arrow right Ala and Pro super(485) arrow right Ala mutants were relatively unaffected. Thus, although mAb413 binds to the same region as **human A2** inhibitors, it recognizes a different set of amino acid side chains. The side chains recognized by **human A2** inhibitors appear to be similar, despite the differing immune settings that give rise to fVIII alloantibodies and autoantibodies.

18/3,AB/10 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus

03099922 JICST ACCESSION NUMBER: 97A0305370 FILE SEGMENT: JICST-E
Anti-factor **VIII** inhibitor alloantibodies recognizing the **A2** domain in the **human** factor **VIII** heavy chain poorly bind to **porcine** factor **VIII**.
SAWAMOTO Y (1); SHIMA M (1); TANAKA I (1); NAKAI H (1); KAMISUE S (1); YOSHIOKA A (1); SCANDELLA D (2)
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Int J Hematol, 1997, VOL.65,NO.2, PAGE.151-158, FIG.6, TBL.1, REF.18
JOURNAL NUMBER: F0888ABI ISSN NO: 0925-5710 CODEN: IJHEE
UNIVERSAL DECIMAL CLASSIFICATION: 616.151/.157 616.11/.16
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DOCUMENT TYPE: Journal
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MEDIA TYPE: Printed Publication
ABSTRACT: Anti-factor **VIII** (FVIII) inhibitor alloantibodies from 11 patients with hemophilia A, along with five anti-FVIII neutralizing monoclonal antibodies, were examined for differences in their reactivities with the **A2** and C2 domains of **human** and **porcine** FVIII. None of the patients had been previously treated with **porcine** FVIII. Six inhibitors which specifically recognized the **human** FVIII C2 domain bound to both the 76-kDa **porcine** FVIII light chain and its 69-kDa proteolyzed fragments, showing cross-reactivity against **porcine** FVIII between 33 and 100%. Two **A2**-specific inhibitors did not react with **porcine** FVIII. The cross-reactivity was low (0-0.5%). The inhibitors recognizing both C2 and **A2** reacted with the 76- and 69-kDa bands of **porcine** FVIII light chain, with cross-reactivity of between 11 and 33%. Monoclonal antibodies recognizing A1 (C-5) and **A2** (JR8) did not react with the **porcine** FVIII. No anti-**porcine** FVIII neutralizing activity was detected in these antibodies. Monoclonal antibodies to the amino-terminal portion of A3 (NMC-**VIII**/10 and C-2) poorly reacted with the 76-kDa band, the cross-reactivities being 0 and 0.5%, respectively. NMC-**VIII**/5 recognizing C2 which competes with the C2-specific inhibitor, reacted with both the 76- and 69-kDa fragments showing cross-reactivity of 13%. These findings suggest that **porcine A2** is antigenically different from **human A2**. The **A2**-specific inhibitor is a useful indicator for therapy with **porcine** FVIII. (author abst.)

18/3,AB/11 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

03796052 H.W. WILSON RECORD NUMBER: BGSA98046052
Biochemistry and genetics of von Willebrand factor.
AUGMENTED TITLE: review
Sadler, J. Evan
Annual Review of Biochemistry v. 67 (1998) p. 395-424
SPECIAL FEATURES: bibl il ISSN: 0066-4154
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 12540

ABSTRACT: Von Willebrand factor (VWF) is a blood glycoprotein that is required for normal hemostasis, and deficiency of VWF, or von Willebrand disease (VWD), is the most common inherited bleeding disorder. VWF mediates the adhesion of platelets to sites of vascular damage by binding to specific platelet membrane glycoproteins and to constituents of exposed connective tissue. These activities appear to be regulated by allosteric mechanisms and possibly by hydrodynamic shear forces. VWF also is a carrier protein for blood clotting factor **VIII**, and this interaction is required for normal factor **VIII** survival in the circulation. VWF is assembled from identical {approximately equal to}250 kDa subunits into disulfide-linked multimers that may be >20,000 kDa. Mutations in VWD can disrupt this complex biosynthetic process at several steps to impair the assembly, intracellular targeting, or secretion of VWF multimers. Other VWD mutations impair the survival of VWF in plasma or the function of specific ligand binding sites. This growing body of information about VWF synthesis, structure, and function has allowed the reclassification of VWD based upon distinct pathophysiologic mechanisms that appear to correlate with clinical symptoms and the response to therapy. With permission, from the Annual Review of Biochemistry Volume 67, 1998, by Annual Reviews Inc. (http://www.annurev.org).

18/3,AB/12 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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14912184 PASCAL No.: 01-0061793
Mapping factor **VIII** inhibitor epitopes using hybrid **human/porcine** factor **VIII** molecules. Discussion
Immune Tolerance in Hemophilia and the Treatment of Hemophiliacs with an Inhibitor
LOLLAR Pete; SCHWARTZ comment; LOLLAR comment; RYPERT comment; LILLICRAP comment; REMY Saint comment; HOYER comment
MARIANI Guglielmo, ed; BRACKMANN Hans-Hermann, ed
Department of Medicine, Emory University, Atlanta GA, United States
Hematology, University of Palermo Medical School, Palermo, Italy;
Institute for Experimental Hematology and Transfusion Medicine, University of Bonn, Bonn, Germany
Workshop on Immune Tolerance, 3 (Palermo ITA) 1999-10
Journal: Haematologica : (Roma), 2000, 85 (10 SUP) 26-30
Language: English
Four epitopes in the factor **VIII** (FVIII) molecule have been identified that constitute the targets for antibodies in most inhibitor plasmas. These epitopes are located in the **A2**, A3 and C2 domains and in the activation peptide (ar3 region) of the FVIII light chain. We have developed a method for mapping FVIII epitopes using recombinant hybrid **human/porcine** FVIII molecuies. Ongoing studies continue to provide higher resolution maps of these epitopes. The manipulation of inhibitor epitopes using recombinant DNA technology may lead to improved forms of FVIII that have lower antigenicity and/or lower immunogenicity.

18/3,AB/13 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal
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13197230 PASCAL No.: 97-0461508
Loss of tolerance to exogenous and endogenous factor **VIII** in a mild hemophilia A patient with an Arg SUP 5 SUP 9 SUP 3 to cys mutation
THOMPSON A R; MURPHY M E P; LIU M; SAENKO E L; HEALEY J F; LOLLAR P; SCANDELLA D
Puget Sound Blood Center and Departments of Medicine & Biological Structure, University of Washington, Seattle, United States; Holland Laboratory, American Red Cross, Rockville, MD, United States; Department of Medicine, Emory University, Atlanta, GA, United States
Journal: Blood, 1997, 90 (5) 1902-1910
Language: English
A 42-year-old patient with mild hemophilia A developed spontaneous muscle hematomas 1 month after intense therapy with factor **VIII** concentrates. Factor **VIII** clotting activity was less than 1% and his factor **VIII** inhibitor was 10 Bethesda units (BU)/mL. The titer peaked at 128 BU despite daily infusions of factor **VIII** ; 1 year later, the titer was 13 BU with no spontaneous bleeding for 4 months. The plasma inhibitor was 95% neutralized by factor **VIII A2** domain but less than 15% neutralized by light-chain or C2 domain. His inhibitor did not cross-react with **porcine** factor **VIII** and was at least 10-fold less reactive to a series of hybrid factor **VIII** proteins in which **human** residues 484-508 are replaced by the homologous **porcine** sequence (Healey et al, J Biol Chem 270:14505, 1995). The inhibitor patient's DNA encoding his **A2** domain and flanking sequences showed a C-T transition predicting Arg SUP 5 SUP 9 SUP 3 to Cys. Thirteen patients from 5 unrelated families with Cys SUP 5 SUP 9 SUP 3 have not developed inhibitors. Factor **VIII** clotting activity from one of them was inhibited similarly to diluted normal plasma by inhibitor patient plasma. In an homologous structure, ceruloplasmin (Zaitseva et al, J Biol Inorgan

Chem 1:15,1996), the residue equivalent to Arg SUP 5 SUP 9 SUP 3 , is in a loop distinct from residues 484-508. On solution phase immunoprecipitation with labeled factor **VIII** fragments, **A2**, light chain, and C2 domains bound. In contrast to typical immune responses to factor **VIII** in patients with severe hemophilia A, this patient's inhibitor was almost entirely reactive with common epitopes within the **A2** domain whereas by more sensitive immunoprecipitation testing antibodies to light chain epitopes were also present. Accordingly, immune responsiveness to exogenous factor **VIII** (antigen burden) appears to be more critical than his endogenous, hemophilic factor **VIII** to his developing high-titer anti-factor **VIII** antibodies and loss of tolerance to both native and hemophilic factor **VIII** proteins.

18/3,AB/14 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

12847826 PASCAL No.: 97-0068259
The cDNA and derived amino acid sequence of **porcine** factor **VIII**
HEALEY J F; LUBIN I M; LOLLAR P
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Journal: Blood, 1996, 88 (11) 4209-4214
Language: English
The cDNA corresponding to 137 bp of the 5' untranslated region, the signal peptide, and the A1, A3, C1, and C2 domains of **porcine** factor **VIII** (fVIII) have been cloned and sequenced. Along with previously determined sequences of the **porcine** fVIII B domain and the **A2** domain, this completes the sequence determination of the cDNA corresponding to the translated protein. Alignments of the derived amino acid sequence of **porcine** fVIII with **human** and murine FVIII indicate that the A1, **A2** , A3, C1, and C2 domains are more conserved than the B domains or the proteolytic cleavage peptides corresponding to residues 337-372 and 1649-1689. The knowledge of the **porcine** fVIII cDNA may be useful to understand functional and immunological differences between **human** and **porcine** fVIII and may lead to improved fVIII replacement products for hemophilia A patients through the development of recombinant **porcine** fVIII or hybrid **human/porcine** fVIII derivatives.

18/3,AB/15 (Item 4 from file: 144)
DIALOG(R)File 144:Pascal

11538705 PASCAL No.: 94-0419150
Isolation and characterization of thrombin-activated **human** factor **VIII**
CURTIS J E; HELGERSON S L; PARKER E T; LOLLAR P
Baxter Healthcare Corp., Baxter Biotech Group, Duarte CA 91010, USA
Journal: The Journal of biological chemistry, 1994, 269 (8) 6246-6251
Language: English
Recombinant **human** factor **VIII** (fVIII) was activated by thrombin at pH 7.4, followed by CM-Sepharose chromatography at pH values ranging from 3.5 to 7.4. Optimal coagulant activity was recovered at pH 5.5 and was associated with the isolation of an A1/**A2** /A3-C1-C2 heterotrimer. The activity was stable at -80 SUP o C, but decayed slowly (t SUB 1 SUB / SUB 2 similar = 1 week) and nonproteolytically at room temperature or 4 SUP o C. The coagulant activity of the pH 5.5 fVIIIa preparation assayed in **human** hemophilia A plasma was only 20% that of **porcine** factor VIIIa. How ever, its activity was approximately 75% that of **porcine** fVIIIa in a plasma-free assay, indicating that